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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 203 582 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
08.05.2002 Bulletin 2002/19

(21) Application number: **00937177.4**

(22) Date of filing: **07.06.2000**

(51) Int Cl.[7]: **A61K 31/18**, A61P 13/02

(86) International application number:
PCT/JP00/03691

(87) International publication number:
WO 01/10436 (15.02.2001 Gazette 2001/07)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **09.08.1999 JP 22505299**

(71) Applicant: **YAMANOUCHI PHARMACEUTICAL CO. LTD.**
Tokyo 103-8411 (JP)

(72) Inventors:
- **SHIMOYAMA, Mitsuru**
  Tokyo 174-8612 (JP)
- **WATANABE, Takeshi**
  Tokyo 174-8612 (JP)
- **FURUDATE, Naomichi**
  Tokyo 174-8612 (JP)

(74) Representative: **HOFFMANN - EITLE**
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München (DE)

(54) MEDICINAL COMPOSITIONS FOR TREATING LOWER UROPATHY

(57) A therapeutic agent for lower urinary tract symptoms containing tamsulosin or a pharmaceutically acceptable salt thereof as an effective ingredient.

EP 1 203 582 A1

Printed by Jouve, 75001 PARIS (FR)

Description

Technical Field of the Invention

[0001] The present invention relates to a pharmaceutical agent and, more particularly, it relates to a therapeutic agent for lower urinary tract symptoms.

Background Art

[0002] Bladder and urethra which are called lower urinary tracts participate in an urinary function and the function is controlled by three kinds of nerves which are sympathetic nerve, parasympathetic nerve and somatic nerve (pudendal nerve) (*Rinsho to Kenkyu*, **71**(5):1180, 1994).

[0003] There are various causative diseases for the urinary disturbance and they have been roughly classified into (1) organic obstruction of urethra and (2) abnormality of urination-controlling nerve (*Brain Nursing,* **15**, No.1, pages 94-93, 1999).

[0004] Examples of (1) organic obstruction of urethra are benign prostatic hyperplasia, urethral stricture, urethral calculus and tumor, etc. With regard to the organic disturbance, the obstruction can be removed by a urologically surgical operation but, because of the risk by the operation and of sequela after the operation, a pharmacotherapy is preferred.

[0005] Urinary disfunction associated with benign prostatic hyperplasia is a disease which occurs only in males and the disturbance is caused by both urethral stricture (mechanical obstruction) due to an oppression of enlarged prostate gland and overconstriction (functional obstruction) of prostatic smooth muscle accompanied by an increase in α_1 receptor in enlarged prostate gland (*Rinsho Kagaku,* **33**(12):1542, 1997). With regard to therapeutic agents therefor, preparations of plant and animal extracts and antiandrogens were used firstly. However, preparations of plant and animal extracts have low effectiveness and, moreover, they have no scientific grounds while antiandrogens have a slow onset of effect and a low efficacy and, moreover, they have a disadvantage of causing a side effect of sexual dysfunction such as impotence. Later, α-adrenaline receptor blockers such as tamsulosin which lower intraurethral pressure by blocking the increased α_1 receptor in the prostatic gland were developed and have been commonly used as the drugs having high effectiveness and high safety.

[0006] Urinary disturbance due to (2) abnormality of urination-controlling nerve is a urinary disturbance occurring both in males and females caused by disorder of sympathetic nerve which controls the operation of urethra and by that of parasympathetic nerve which controls the operation of bladder, and is generally called neurogenic bladder. Main diseases which result in the neurogenic bladder are encephalopathy such as cerebrovascular accident, Parkinsonism and brain tumor; myelopathy such as myelic injury, spina bifida, ossification of the posterior longitudinal ligament, HAM and tethered cord syndrome; peripheral nerve disturbance such as diabetes mellitus, operation in pelvic cavity and stricture of lumber vertebral canal; and others such as multiple sclerosis and spinocerebellar degeneracy (*Hyojun Hinyokikigaku* [= Textbook of Urology], fifth edition, published in 1998).

[0007] With regard to therapeutic agents therefor, there have been attempts for the use of cholinolytics with an object of relaxation of bladder, cholinergics with an object of potentiating the constriction of bladder, and α receptor blockers with an object of lowering the intraurethral pressure. The present applicant has already confirmed that tamsulosin or a salt thereof is clinically effectively for the therapy of neurogenic bladder (PCT/JP99/03343).

[0008] On the other hand, in recent years, urinary disturbance which does not correspond to any of apparent organic disturbance and neurological abnormality in lower urinary tracts has been called (3) lower urinary tract symptoms and is being established as a new and third classification for urinary disturbance in addition to (1) organic obstruction of urethra and (2) abnormality of urination-controlling nerve. The causative diseases therefor will be dysuria, urinary neck sclerosis, urinary neck obstruction, urethral syndrome, detrusor-sphincter incoordination, unstable bladder, chronic prostatitis, chronic cystitis, prostatic cancer, Hinman syndrome, Fowler syndrome, psychogenic urinary disturbance, drug-induced urinary disturbance, urinary disturbance due to aging, etc. and urinary disturbance of females is also included therein. However, mechanism of the diseases has not been fully clarified yet and no therapeutic method has been established yet.

[0009] At present, there is no pharmaceutical agent in Japan, Europe and America which has been clinically established as a therapeutic agent for lower urinary tract (which is the urinary disturbances as the said third group) having an efficacy. There has been a brisk demand for development of therapeutic agent for the lower urinary tract symptoms.

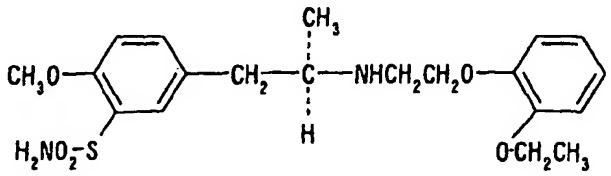
Disclosure of the Invention

[0010] Under such circumstances, the present inventor has found that tamsulosin or a salt thereof is effective for the therapy of lower urinary tract symptoms which are the urinary disturbances of the third group.

[0011] Thus, the present invention relates to a pharmaceutical composition for the therapy of lower urinary tract symptoms where said composition contains tamsulosin or a pharmaceutically acceptable salt thereof.

[0012] The present invention further relates to the use of tamsulosin or a pharmaceutically acceptable salt thereof for the manufacture of a therapeutic agent for lower urinary tract symptoms. The present invention furthermore relates to a method for the therapy of lower urinary tract symptoms where said method includes administration of tamsulosin or a pharmaceutically acceptable salt thereof to a patient.

[0013] The chemical name of tamsulosin is (R)(-)-5-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene-sulfonamide and is represented by the following structural formula. Tamsulosin has been firstly disclosed in the Japanese Patent Laid-Open No. Sho-56/110665 together with its pharmaceutically acceptable salts.



[0014] Tamsulosin or a salt thereof has been known to have an adrenaline α_{1A} receptor blocking action and, particularly, its hydrochloride (tamsulosin hydrochloride) has an α_1 receptor blocking action for the areas of urethra and prostatic gland and has been commonly used as a pharmaceutical agent which lowers the pressure of prostatic gland part of the intraurethral pressure curve and improves the urinary disturbance accompanied by prostatic hypertrophy.

[0015] However, there has been no report confirming the efficacy to lower urinary tract symptoms having different onset mechanism. Now the present inventor has clinically confirmed for the first time that tamsulosin hydrochloride is effective for the therapy of lower urinary tract symptoms.

[0016] The present invention will be illustrated in detail as hereunder.

[0017] In the present invention, the term "lower urinary tract symptoms" stands for a concept which is a symptom of urinary disturbance due to a functional obstruction of lower urinary tract of both males and females and does not include that which is due to disturbance of nerve controlling the lower urinary tract and that which is due to an organic disturbance of the lower urinary tract. Fig. 1 shows the positioning of the lower urinary tract symptoms in urinary disturbance in terms of classification to clearly show the concept of the said disease.

[0018] A therapeutic agent for lower urinary tract symptoms is a pharmaceutical agent which treats the lower urinary tract symptoms and/or a pharmaceutical agent which improves the symptom of the lower urinary tract symptoms. A pharmaceutical composition for the therapy of lower urinary tract symptoms contains an effective ingredient which treats the lower urinary tract symptoms and/or improves the symptom of the lower urinary tract symptoms and pharmaceutically acceptable carriers thereof.

[0019] Tamsulosin and its pharmaceutically acceptable salt are easily available by means of the methods described in the Japanese Patent Laid-Open Nos. Sho-56/110665 and Sho-62/114952 or the methods similar thereto.

[0020] Tamsulosin is able to form pharmaceutically acceptable acid- and base-addition salts with a wide range of inorganic and organic acids or bases. Such salts also constitute a part of the present invention. Their examples are salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid; salts with organic acids such as fumaric acid, malic acid, citric acid, succinic acid; salts with alkaline metals such as sodium, potassium; and salts with alkaline earth metals such as calcium, magnesium, etc. In the present invention, hydrochlorides are most preferred. Such salts can be manufactured by a conventional method.

[0021] The pharmaceutical agent of the present invention can be prepared as oral solid preparations, oral liquid preparations or injection preparations by a conventional method using organic or inorganic carrier, filler and other additives suitable for oral or parenteral administration. Preferred ones are oral solid preparations which can be easily administered by a patient himself/herself and are convenient for preservation and carrying and, to be more specific, they are tablets, diluted powder, granules, fine granules, capsules, pills, etc.

[0022] In such solid preparations, the active substance is mixed with at least one inert diluent such as lactose, mannitol, glucose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate. The composition may-contain additives other than the inert diluent according to a conventional method and their examples may be binders such as hydroxypropyl cellulose and hydroxypropylmethyl cellulose; lubricants such as magnesium stearate, calcium stearate, polyethylene glycol, starch and talc; disintegrants such as calcium cellulose glycolate; stabilizers such as lactose; solubilizing aids such as glutamic acid and aspartic acid; plasticizers such as Tween 80 and triacetin; and coloring agents such as titanium oxide and iron sesquioxide. If necessary, tablets or pills may be coated with a sugar coat or with a film of a gastric or an enteric substance such as sucrose, gelatin, agar, pectin, hydroxypropyl

cellulose and hydroxypropylmethyl cellulose.

[0023] The most preferred preparation in the present invention is a sustained-release preparation of a sustained releasing type. The sustained-release preparation may be made into tablets, granules, fine granules or capsules by a known method. The sustained-release preparation is prepared by coating tablets, fine granules, fine granules or capsules with, for example, fat/oil, fatty acid ester of polyglycerol, hydroxypropyl cellulose, etc. by a known method.

[0024] The sustained-release preparation disclosed in the Japanese Patent Laid-Open No. Sho-62/9 is particularly preferred. Thus, in each unit preparation, particles which are prepared by granulation after adding an elution suppressor to a mixture of an active compound and not less than 50% by weight of a unit-forming substance in a unit are filled in a capsule to prepare a capsule preparation or to prepare a tablet by a conventional method. With regard to the elution suppressor, a water-insoluble high-molecular substance such as an acrylic polymer, copolymer or cellulose derivative is used and it is appropriate that the elution suppressor is used, for example, in a form of an aqueous suspension, an aqueous emulsion or a solution in a water-containing organic solvent. Examples of the commercially available one are Eudragit L 30D55 (methacrylic acid copolymer LD), Eudragit E 30D (emulsion of copolymer of ethyl acrylate with methyl methacrylate) and Aquacoat ECD-30 (aqueous suspension of ethyl cellulose) and they may be used as elution suppressors either as they are or after diluting with water if necessary.

[0025] Dose of tamsulosin or a pharmaceutically acceptable salt thereof is appropriately decided for each case taking administering route, symptom of the disease, age and sex of the object to be treated, etc. into consideration. In the case of an oral administration, tamsulosin hydrochloride is administered to an adult usually in a dose of about 0.1 to 0.8 mg/day or, most preferably, in a dose of 0.2 to 0.4 mg/day and that is administered *per os* after meals once daily.

[0026] Incidentally, the pharmaceutical agent of the present invention is well effective by its sole administration but it is also possible that a cholinergic agent, a cholinolytic agent or other central nerve drug is used together either simultaneously or with a time interval.

Brief Explanation of the Drawings

[0027] Fig. 1 shows the positioning of the lower urinary tract symptoms in urinary disturbance in terms of classification.

Best Mode for Carrying Out the Invention

[0028] The present invention will now be illustrated in more detail by way of Examples and Test Examples as hereunder although the present invention is not limited to those Examples, etc.

Example 1.

[0029] 5 g of tamsulosin hydrochloride and 470 g of crystalline cellulose were well mixed, 500 g of a mixture of 83.3 g of Eudragit L30D-55 (25 g as a solid) with water were added thereto and the mixture was granulated using a high-speed stirring granulator. The resulting particles were in a spherical shape having a particle size of 0.1-1.5 mm where most of them were 0.2-1.0 mm.

[0030] The resulting particles were mixed with talc and magnesium stearate and filled in capsules to prepare capsule preparations (containing 0.2 mg of tamsulosin hydrochloride in a capsule).

Examples 2-6.

[0031] The same process as in Example 1 was conducted whereby the particles manufactured according to the formulations of Table 1 were made into capsule preparations.

Table 1 (unit: grams)

Example Number	Tamsulosin Hydrochloride (g)	Crystalline Cellulose (g)	Eudragit L30D-55 (Solid Content) (g)
2	5	445	166.6 (50)
3	5	395	333.3(100)
4	5	482.5	41.7 (12.5)
5	2.5	472.5	83.3 (25)
6	1.25	473.75	83.3 (25)

Example 7.

[0032] 5 g of tamsulosin hydrochloride, 420 g of crystalline cellulose and 50 g of magnesium stearate were well mixed, a mixture of 83.3 g of Eudragit L30D-55 (25 g as a solid) with water were added thereto and the mixture was kneaded followed by granulating by a centrifugal fluid granulator. The resulting particles were in a spherical shape having a particle size of 0.1-1.5 mm where most of them were 0.2-1.0 mm.

[0033] The resulting particles were mixed with talc and magnesium stearate and filled in capsules to prepare capsule preparations (containing 0.2 mg of tamsulosin hydrochloride in a capsule).

Examples 8-10.

[0034] The same process as in Example 7 was conducted whereby the particles manufactured according to the formulations of Table 2 were made into capsule preparations.

Table 2 (unit: grams)

Example Number	Tamsulosin Hydrochloride	Crystalline Cellulose	Magnesium Stearate	Eudragit L30D-55 (Solid Content)
8	5	460	10	83.3 (25)
9	5	445	25	83.3 (25)
10	2.5	462.5	10	83.3 (25)

Example 11.

[0035] 80 g of hydrogenated castor oil was melted, 10 g of tamsulosin hydrochloride and 30 g of hydroxypropyl cellulose having a low degree of substitution were dispersed therein and the dispersion was made into fine particles by means of a spray condyling. The resulting fine particles (60 g) were well mixed with 440 g of crystalline cellulose, 500 g of water were added thereto and the mixture was granulated using a centrifugal fluid granulator.

[0036] The resulting particles were mixed with talc and magnesium stearate and filled in capsules to prepare capsule preparations.

[0037] Test Example 1. Clinical Test to Patients Suffering from Lower Urinary Tract Symptoms (a four-week test)

[0038] A clinical test was carried out under the following conditions using the patients suffering from lower urinary tract symptoms. (cf. Chapter 1: Indexes for Evaluation of Prostatic Hypertrophy in "Guideline for Clinical Test for Urinary Disturbance" published by Iyaku Tosho Shuppan)

[0039] Subjects: four patients diagnosed as lower urinary tract symptoms, i.e. urinary disturbance without clear organic or neurological abnormality in lower urinary tract (3 males and 1 female).

[0040] Test drug and administering method: One capsule containing 0.2 mg of tamsulosin hydrochloride was orally administered once daily after breakfast.

Test period: four weeks (28 days)
Observed items: Evaluations and measurements were made for the following items before and after the administration.

(1) Total score for subjective symptoms

[0041] Questioning was done to the patients for the following items and the total score was obtained.

<1> Feel of residual urine

[0042] "How often do you have a sensation of not emptying your bladder completely after you finished urinating?"

0: not at all
1: not so often
2: sometimes
3: about half the time
4: often
5: almost always

<2> Urination within two hours

[0043] "How often do you have to urinate again less than two hours after you finished urinating?"

0: not at all
1: not so often
2: sometimes
3: about half the time
4: often
5: almost always

<3> Break of urinary stream

[0044] "How often do you find you stopped and started again several times when you urinated?"

0: not at all
1: not so often
2: sometimes
3: about half the time
4: often
5: almost always

<4> Urgency

[0045] "How often do you find it difficult to postpone urination?"

0: not at all
1: not so often
2: sometimes
3: about half the time
4: often
5: almost always

<5> Force of urinary stream

[0046] "How often do you have a weak urinary stream?"

0: not at all
1: not so often
2: sometimes
3: about half the time
4: often
5: almost always

<6> Straining upon urination

[0047] "How often do you have to push or strain to begin urination?"

0: not at all
1: not so often
2: sometimes
3: about half the time
4: often
5: almost always

<7> Frequency of urination at night

[0048] "How many times do you most typically get up to urinate from the time you go to bed at night until the time

you get up in the morning?"

0: none
1: one times
2: two times
3: three times
4: four times
5: five or more times

[0049] The results of the observed items before and after the test are shown in Table 3.

Table 3

sex	age	Total score for subjective symptoms		
		before the test	after the test	Changing Rate (%)
female	54	15	11	-26.7
male	69	26	9	-65.4
male	62	25	13	-48.0
male	47	26	20	-23.1
avg.	58.0	23.0	13.3	-40.8

*)Changing Rate(%) = [(Total score for subjective symptoms after the test) - (Total score for subjective symptoms before the test)] ÷(Total score for subjective symptoms before the test)×100

(2) QOL Index

[0050] With regard to an index for quality of life (QOL), a questioning that "How do you think if the present urinary condition continues in future as well?" was done as a total diagnosis concerning the urinary disturbance and any of the following evaluations was collected.

0: quite satisfactory
1: satisfactory
2: generally satisfactory
3: neither satisfactory nor unsatisfactory
4: a bit unsatisfactory
5: unsatisfactory
6: quite unsatisfactory

[0051] The result was that the mean value for the patients before the administration was 4.8 while that after the administration was 3.8 whereby there was an improvement of one point in average in terms of the QOL index.

[0052] From the above result, tamsulosin hydrochloride showed improvements in (1) the total score for subjective symptom and (2) the QOL index for the patients suffering from lower urinary tract symptoms whereby tamsulosin hydrochloride was confirmed to be effective as a therapeutic agent for lower urinary tract symptoms.

[0053] Test Example 2. Clinical Test to Patients Suffering from Lower Urinary Tract Symptoms (a twelve-week test)

[0054] A clinical test was carried out under the following conditions using the patients suffering from lower urinary tract symptoms.

[0055] Subjects: eighteen patients diagnosed as lower urinary tract symptoms, i.e. urinary disturbance without clear organic or neurological abnormality in lower urinary tract (15 males and 3 female, age:57.2±14.2).

[0056] Test drug and administering method: One capsule containing 0.2 mg of tamsulosin hydrochloride was orally administered once daily after breakfast for four weeks and, after that, the dose after 4 weeks was controlled in consideration of the following criterion, and the dose was orally administered once daily after breakfast.

<Criterion of Dose after 4 weeks>

[0057]

side effects	Changing Rate of Total score for subjective symptoms in 4 weeks	dose of after 4 weeks
yes		0.2mg/day
no	Changing Rate of Total score for subjective symptoms ≦ -25.0%	
	Changing Rate of Total score for subjective symptoms ≧ -24.9%	0.4mg/day

[0058] Test period: twelve weeks (84 days)(4 weeks(28 days) for 8 males)

[0059] Observed items: Evaluations and measurements were made for the following items before and after the administration.

(1) Total score for subjective symptoms

[0060] Total scores for the following <1>~<7> before and after the administration were obtained in the same way as in Test Example 1.

[0061] <1> Feel of residual urine, <2> Urination within two hours, <3> Break of urinary stream, <4> Urgency, <5> Force of urinary stream, <6> Straining upon urination and <7> Frequency of urination at night.

(2) QOL Index

[0062] "How do you think if the present urinating state continues in future as well?"

0: quite satisfactory
1: satisfactory
2: generally satisfactory
3: neither satisfactory nor unsatisfactory
4: a bit unsatisfactory
5: unsatisfactory
6: quite unsatisfactory

(3) Test on Functions

<1> maximum urinary stream rate

<2> average urinary stream rate

[0063] The results of the observed items after the test are shown in Table 4.

Table 4

the observed items		after 4 week	after 12 week
Changing Rate of Total score for subjective symptoms	male	-43.0±26.5% (n=15)	-47.0±35.6% (n=7)
	Female	-30.5±16.9% (n=3)	-37.4±26.8% (n=3)
	Total	-40.9±25.2% (n=18)	-44.6±32.1% (n=10)
Changing Amt of QOL Index	male	-1.6±1.8 (n=15)	-2.9±1.9 (n=7)
	Female	-1,3±1.2 (n=3)	-3.0±1.7 (n=3)
	Total	-1.6±1.7 (n=18)	-2.9±1.7 (n=10)
Changing Amt of Maximum urinary stream rate	male	+2.9±7.4ml/s (n=15)	+7.8±4.3ml/s (n=7)
	Female	+ 3.8 ±1.9ml/s (n=3)	+ 6.2±6.0ml/s (n=3)
	Total	+3.1±6.7ml/s (n=18)	+7.3±4.6ml/s (n=10)

Table 4 (continued)

the observed items		after 4 week	after 12 week
Changing Amt of Average urinary stream rate	male	+1.9±3.6ml/s (n=15)	+4.6±2.2ml/s (n=7)
	Female	+2.2±1.8ml/s (n=3)	+2.1±2.8ml/s (n=3)
	Total	+2.0±3.3ml/s (n=18)	+3.8±2.5ml/s (n=10)

[0064] The results after 12 weeks in this test are decided by "Guideline for Clinical Test for Urinary Disturbance" that the effective rate(Degree of Improvement as a whole is more than "Useful") is 70.0%.

[0065] From the above result, tamsulosin hydrochloride showed improvements in (1) the total score for subjective symptom, (2) the QOL index and (3) test on functions for the patients suffering from lower urinary tract symptoms whereby tamsulosin hydrochloride was confirmed to be effective as a therapeutic agent for lower urinary tract symptoms.

Industrial Applicability

[0066] In accordance with the present invention, there is provided a clinically effective and good therapeutic agent for lower urinary tract symptoms.

Claims

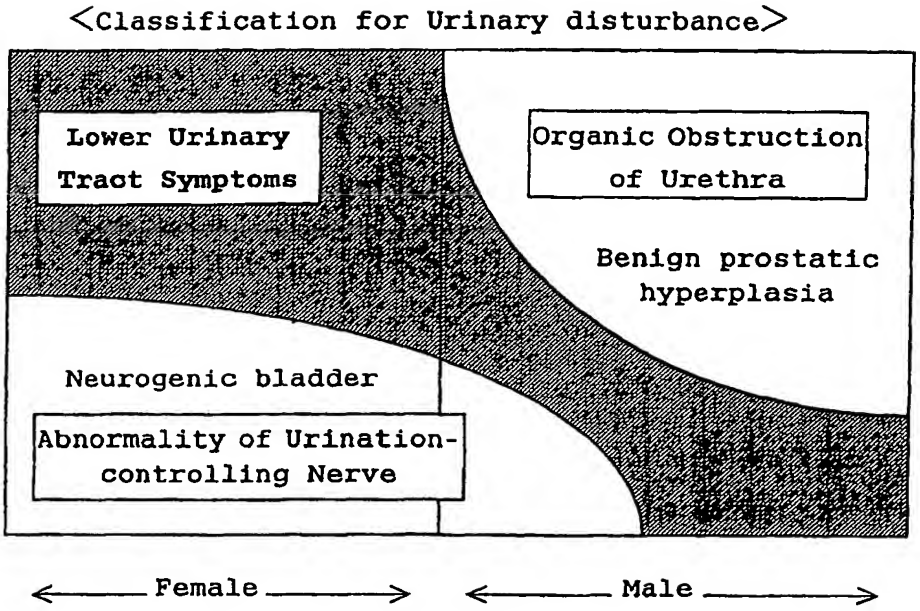
1. A pharmaceutical composition for the therapy of lower urinary tract symptoms where said composition contains tamsulosin or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition for the therapy of lower urinary tract symptoms according to claim 1 in which said composition contains tamsulosin hydrochloride.

3. The use of tamsulosin or a pharmaceutically acceptable salt thereof for the manufacture of a therapeutic agent for lower urinary tract symptoms.

4. A method for the therapy of lower urinary tract symptoms where said method includes administration of tamsulosin or a pharmaceutically acceptable salt thereof to a patient.

Fig.1


<Classification for Urinary disturbance>
Lower Urinary Tract Symptoms
Organic Obstruction of Urethra
Benign prostatic hyperplasia
Neurogenic bladder
Abnormality of Urination-controlling Nerve
Female
Male

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/03691

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K31/18, A61P13/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K31/18, A61P13/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, 416804, A1 (YAMANOUCHI PHARMACEUTICAL CO.LTD.), 13 March, 1991 (13.03.91), (especially, page 3, lines 4 to 12,) & JP, 3-173816, A & AT, 89719, E & ES, 2058807, T3 & CA, 2024438, A	1-3
X	MC Michel et al."Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms", Prostate Cancer and Prostatic Diseases, Vol.1 (1998) pp.332-335	1-3
X	P.ABRAMS et al., "A dose-ranging study of the efficacy and safety of tamsulosin, the first prostate-selective α_{1A}-adrenoceptor antagonist, in patients with benign prostatic obstruction (symptomatic benign prostatic hyperplasia)", British Journal of Urology, Vol.80 (1997) pp.587-596	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August, 2000 (11.08.00)	29 August, 2000 (29.08.00)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/03691

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4
because they relate to subject matter not required to be searched by this Authority, namely:

It pertains to methods for treatment of the human body by therapy (Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)